ULTRASOUND-BASED ELASTOGRAPHY: PRINCIPLES AND CLINICAL APPLICATIONS

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Abstract— **Ultrasound-based elastography is a non-invasive medical imaging technique that provides an estimation of tissue stiffness. In the past decade, researchers have explored the potential use of ultrasound-based elastography in diagnosing abnormal organs based on the obtained stiffness value. This article details the physics and principle of ultrasound-based elastography as well as the clinical applications of this technology at various anatomic structures.**

Keywords— **2-dimentional Shear Wave Elastography, Point Shear Wave Elastography, Transient Elastography, Stiffness, Strain Elastography.**

I. Introduction

Manual palpation is a core skill in physical assessment. General physicians typically use digital palpation to assess the elasticity properties of a tissue, referred to as stiffness in the detection disease tissue. The elasticity properties of tissue often change in pathological condition. Fibrosis is a pathological state where excessive deposition of extracellular matrix (ECM) in organs occurs, which commonly accompanies chronic diseases in many organs, such as the liver and kidney [1] . Production of ECM occurs as a reaction against injury, and fibrosis itself is intrinsically a process to promote tissue repair. However, fibrosis can deteriorate the function of the affected organ if it occurs in excess. Organs with established fibrosis are mechanically stiffer as a result of increased collagen and elastin cross-linking [2]. However, manual palpation assessments are subjective, and little is known about their accuracy or repeatability. Recently, researchers have developed alternative techniques to quantify tissue elasticity.

II. Methods of tissue elasticity evaluation

Elasticity or stiffness is the ability of a deformed object to return to its original shape after the deformation forces are removed. There are two methods of applying external force - the quasi-static and dynamic methods [3]. In quasi-static elastography, a constant stress σ is slowly applied (equal to an external force per unit area) to tissue. Consequently, strain, ε, defined in Equation 1, is obtained by spatial differential of displacement, Δ_2- Δ_1 which is the ratio of the difference in displacement between the two points to the original length, L (Fig. 1):

$$\varepsilon = \frac{\Delta_2 - \Delta_1}{L} \quad (1)$$

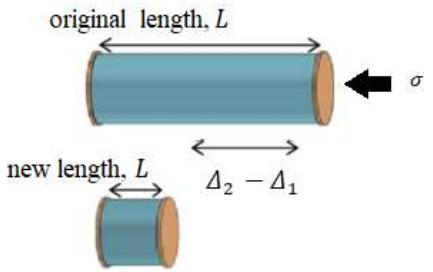

Fig 1 The rod compressed under stress to a new length. The strain is the ratio of this small deformation to the rod's original length.

Stress is always normal in the case of a change in length or volume of a medium. When linearity is satisfied, stress and strain exhibit proportionality, as shown by Hooke's law and its coefficient is referred to as the elastic modulus. There are three types of elastic modulus: Young's modulus (YM), shear modulus, and bulk modulus, as defined on the basis of the method of deformation and is expressed in pressure units - Pascals, or more commonly kPa [4].

Young's modulus, E is defined in Equation 2 when normal stress (quotient of the tensile force divided by the cross-sectional area) σ is applied longitudinally to a long, thin cylindrical object. The strain (the change in length divided by original length) ε_L occurs as shown in Fig. 2a [3] [4].

$$\mathrm{E} = \frac{\sigma}{\varepsilon_L} \quad (2)$$

When the applied stress is tangential to the surface due to the application of force parallel to the surface, then the stress is called shear stress, σ. The shear modulus, G is defined in Equation 3 for the shear deformation shown in Fig. 2b [4].

$$G = \frac{\sigma}{\varepsilon_s} \quad (3)$$

in which, ε_s is shear strain.

When a normal stress is applied from all the sides and changes the volume of a medium, it is called volume or bulk stress, σ. The bulk modulus, B is defined in Equation 4 for the change of volume shown in Fig. 2c.

$$B = \frac{\sigma}{\left(\frac{\Delta V}{V}\right)} \quad (4)$$

where ΔV is change volume (m^3) and V is original volume (m^3).

In dynamic methods, an external force, either a short transient mechanical force or an oscillatory force with a fixed frequency, is applied to tissue [3]. Although the ordinary ultrasound pulse–echo imaging uses longitudinal waves, transverse waves (shear waves) are used for elasticity evaluation. Using the shear modulus G, the speed V_s of shear waves is expressed in Equation 5.

$$V_s = \sqrt{G/\rho} \quad (5)$$

where ρ indicates the density of the medium [4]. Based on the equation, the larger the G (the stiffer the medium is), the faster the wave propagation.

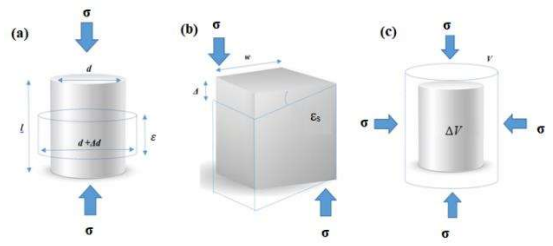

Fig I Three types of deformation: (a) deformation by normal stress, (b) deformation by shear stress and (c) deformation by bulk stress (*d*: diameter, *l*: length, *w*: width, ε_L: strain, ε_s: shear strain, *V*; original volume, *ΔV*: change volume).

III. Principles of Ultrasound Elastography

Ultrasound-based elastography techniques is a new non-invasive medical imaging technique that provides an estimation of tissue stiffness by measuring the degree of distortion caused by soundwaves. It is divided into strain and shear wave elastography techniques. There are three types of shear wave elastography, which includes transient elastography, point shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D SWE)[5].

Strain Elastography

Strain ultrasound elastography is also named real-time ultrasound elastography (RTE) and is the most widely available type of strain ultrasound elastography. A deformation force either by the precompression with the transducer or by physiological movements, such as breathing or heartbeat is applied to tissues, resulting in changes in dimensions and shape [6]. Most of the displacement will be in the direction of the propagation of the ultrasound pulse. The displacement is obtained by calculating the correlation between the echo signal, before and after compression. Multiple images are recorded using conventional imaging at standard frame rates. The relative deformation (strain) is estimated using tissue Doppler techniques. This results in the elastographic image which appears as a colour-coded image superimposed on the B-mode image and displayed next to it on the screen [7].

The intensity of the operator's free-hand pressure is displayed with a numerical scale. As such, the operator can assess the validity of the compression cycles in real-time. This technique allows a qualitative and a semi quantitative assessment of tissue elasticity. The qualitative assessment of the elastography images, also known as elastogram, represents a mapping of the amount of tissue strain at each location [7].

Colour coding depends on the system and usually red represents hard, stiff tissue (small deformation, lowest elastic strain or no strain) and blue represents soft tissue (large deformation, greatest elastic strain) (Fig. 3). There is also a semi quantitative measurement method (the strain ratio), which represents the ratio of strains of the ROI to an equally measuring area in the reference tissue [8]. Two ROIs are manually applied on the screen, one on the target tissue and the second on the reference normal tissue allowing the calculation of their strain ratio by the immediate real-time ultrasound machine analysis.

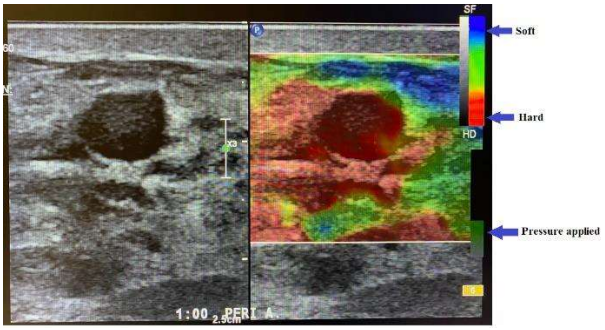

Fig 3 Display method of an elastogram. The translucent colour-coded elastogram within the ROI is superimposed on the corresponding B-mode image.

Clinical Applications of Strain Elastography

Strain elastography has been widely applied in the breast imaging [9]. One of the largest published studies on visual score on strain elastography was conducted on 1786 non-palpable breast masses by Yi et al. [10]. This study applied elasticity scores (5-point) that were based on the visual assessment of the degree and distribution of strain in the hypoechoic mass and surrounding tissue. The mean elasticity score of malignant lesions was higher than that of benign lesions (2.94±1.10 vs. 1.78± 0.81). In the decision to biopsy, strain elastography has higher specificity than B-mode ultrasound in the differentiation between benign and malignant masses and has the potential to reduce biopsies with benign results. Although the results were encouraging, however, authors highlighted that the sonoelastography score, which was based on the B-mode ultrasound findings

was the main limitation of strain elastography. Thus, studies were conducted to evaluate the diagnostic value of semi-quantitative parameters *(i.e.*, strain pattern, width ratio, strain ratio) in differentiating between benign and malignant breast masses [11, 12].

According to Alhabshi et al [11], the semi-quantitative assessment with strain ratio and width ratio in strain elastography were useful parameters in differentiating a benign lesions from a malignant lesions. They proposed a cut-off point values for width ratio of more than 1.1 and strain ratio of more than 5.6 showed a high predictive value of malignancy with specificities of 84% and 76%, respectively ($p < 0.001$). However, operator dependence is a recognised pitfall of ultrasound elastography especially when using the strain method [12]. Moreover, the YM cannot be calculated by strain elastography because the force applied is operator dependent and unknown. Furthermore, this technique is limited to superficial organs only, such as the thyroid and breast because the force applied by the operator is insufficient to deform the deeper organ such as the liver.

Shear Wave Elastography

A shear wave is a slow wave and propagates by creating a tangential 'sliding' force between tissue layers. Shear waves are explicitly related to tissue stiffness. To quantify tissue stiffness in kPa, the YM from Equation 2 can be derived into Equation 6, where V_s is the shear wave velocity and ρ is tissue density.

$$\frac{\sigma}{\varepsilon_L} = 3\rho V_s^2 \qquad (6)$$

Transient Elastography

Transient elastography works by measuring the transmitted spherical shear wave to the surface of the medium, produced by a vibrating actuator that attached on a single-element ultrasound transducer (Fig. 4a) [13].

The displacements induced by the shear wave are tracked using ultrasonic waves generated and received by the single-element ultrasound transducer. The displacement generated, which is a function of depth and of time, is thus estimated by correlations of retro-diffused echoes (via ultra-sound speckle) recorded at a framerate higher than one thousand time per second with a mono-dimensional ultra-sound transducer (5 MHz)[14]. By measuring the phase of each depth, the system manages to extract the phase speed of the shear wave at the central frequency. The results are converted to YM in unit kPa.

Clinical Applications of Transient Elastography

Early detection of cirrhosis by detection of fibrosis is a key element to manage treatment, monitor disease progression, and assess response to therapy. The development of transient elastography provides clinicians with a non-invasive and accurate tool to estimate liver fibrosis. Study from Serra-Burriel, et al. [15] involved six prospective cohorts in Europe and Asia with a total of 6295 patients. They proposed a 9.1 kPa transient elastography cut-off provided the best accuracy for the diagnosis of significant fibrosis (≥F2) in general population settings, whereas a threshold of 9.5 kPa was optimal for populations at-risk for alcoholic liver disease. Additionally, their results showed that transient elastography performed better than serum biomarkers for fibrosis detection using liver biopsy as reference standard. Due to its outstanding diagnostic performance reported by numerous studies, it is likely that liver stiffness examination (LSE) by transient elastography will be widely used in liver units. Therefore, the reproducibility of transient elastography from different observers is crucial.

Boursier, et al. [16] evaluated the learning curve characteristics of liver stiffness with transient elastography in five novice observers with different professional status among hospital staff. Results showed that LSE assessed by transient elastography presents no learning curve effect. A novice observer can perform a reliable LSE after an initial training session (devoted to device presentation and one LSE demonstration by the expert). Time taken to perform LSE also progressively decreases because of a progressive increase in success rate. However, novice–expert agreement for LSE results varied with liver stiffness level in which a poor interobserver agreement for expert LSE < 9 kPa and an excellent agreement for expert LSE > 9 kPa. Although transient elastography provides quantitative measurement, it does not provide grayscale ultrasound images (Figure 4b). Without the ultrasound image guidance, placing the transducer would become challenging, especially for obese patients or patient with narrow intercostal space [17]. Moreover, transient elastography is not capable of obtaining adequate results in patients with ascites. These limitations could affect the reproducibility of transient elastography. Another limitation of this technique is it only limited to liver and spleen study.

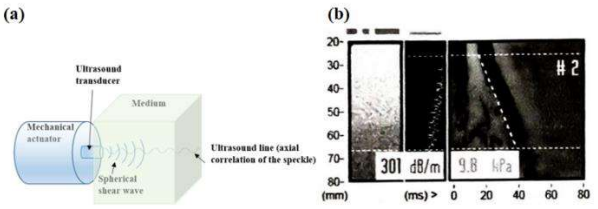

Fig 4 (a) Adjustable low frequency pulse from 10Hz to 500 Hz is generated by the vibrator in the medium thus creating shear waves (Gennisson, 2013). (b) Transient elastography indicates 9.8 kPa for liver stiffness. Note that no anatomical image is shown in transient elastography.

Point Shear Wave Elastography (pSWE)

pSWE uses the acoustic radiation force impulse (ARFI) or acoustic radiation force to generate shear waves in a single focal location that propagate perpendicular to the main ultrasound beam, away from the original region of excitation. The speed of propagation of the shear waves of a homogeneous and isotropic target is directly proportional to

the density and to the shear modulus of the tissue (elasticity). Thus, for a given density, a radiation force moves farther at the focal spot of soft tissues than stiffer tissues, presenting a lower shear modulus and taking longer to reach their maximum deformation, with slower recovery [18].

Meanwhile a low-intensity tracking ultrasound beams are continuously emitted parallel to the main beam to monitor tissue displacement (Fig. 5). To obtain a series of data concerning the tissue response, such as the time-to-peak displacement and the recovery time, the tracking beams intercept the shear wave at several predetermined locations and time intervals [18]. From these data obtained mainly through time-of-flight algorithms (time taken for the wave to travel a distance through a medium), quantitative estimates of shear waves propagation speed and the resultant and tissue stiffness are obtained [3].

Clinical Applications of pSWE

Unlike transient elastography, pSWE is integrated into a conventional ultrasound device. One of the benefits of this technique is that it permits the quantitative measurements of the liver while providing grayscale ultrasound images. Furthermore, pSWE generates shear waves within the targeted structure, thus, adequate results for patients with ascites could be obtained. For the past decade, several meta-analyses of measurements of liver stiffness in patients' chronic liver diseases using pSWE and transient elastography have been published [19-21]. Researchers concluded that pSWE seems to be modestly accurate in detecting significant fibrosis with similar predictive value to transient elastography for significant fibrosis and cirrhosis. However, compared to transient elastography, pSWE is able to obtain reliable measurements thrice higher than transient elastography [20]. Due to the promising results, researchers have extended the application of pSWE to renal imaging.

Studies have shown positive correlation between stiffness values of renal and glomerular filtration rate (GFR) [22-24]. A clear relationship seems to emerge between stiffness values and the degree of fibrosis. According to Yang, et al. [25] and Wang, et al. [26], patients with a severe grade of interstitial fibrosis had a higher SWV compared to moderate and mild grades. Leong, et al. [27] revealed that glomerular sclerosis, interstitial fibrosis, and tubular atrophy are associated with an increase in kidney stiffness, measurable using pSWE. A YM cut-off value equal or more than 5.81 kPa indicates a moderately impaired kidney. However, these results were contradicted by [28, 29] in which a lower stiffness values were observed in patient with deranged GFR and severe grade of interstitial fibrosis. Inconsistent results from pSWE renal imaging likely due to certain limitations from this technique.

The kidney has a complex architectural whereby its mechanical properties varied according to the measurement direction. This is known as anisotropy. Kidney anisotropy has a significant impact on the propagation speed of shear wave in which affects the stiffness measurement obtained. In pSWE, the region of interest (ROI) size is fixed and only allows single stiffness measurement at a time. Patients may find it difficult to hold their breath for a long time if more image acquisitions are needed. Thus, slight changes in breath hold pattern from the patient or unintentionally include the renal medulla in the ROI by the operator could increase measurement variability. Similarly, to transient elastography, pSWE is only applicable to deep structure.

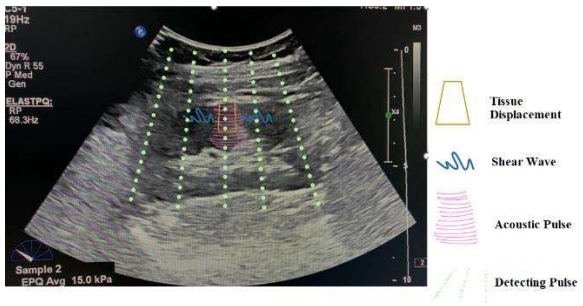

Fig 5 Acoustic pulses are generated together with the main ultrasound beam. The Acoustic pulses induce tissue displacement in a single focal zone to produce shear waves, which propagate perpendicular to the main ultrasound beam [18].

Two-dimensional Shear Wave Elastography (2D SWE)

In this technique, ARFI is used to induce tissue displacement in multiple focal zones which are interrogated in rapid succession. ARFI moves faster than the shear waves thus allowing the ultrasound beam successively focusing at different depths. The different spherical waves generated for each focal beam interfere constructively along a Mach cone, creating two quasi plane shear wave fronts propagating in opposite directions [3] (Fig. 6Fig).

The use of constructive interferences increases their amplitude and improves their propagation distance. When the wave touches the targeted tissue, the tissue is pushed in the direction of propagation, causing the tissue to deform or displace. Since shear wave is induced in multiple focal zones in the tissue with no external vibrator required to generate it, SWE depends on the measurement of the shear wave propagation speed in soft tissue [30]. Based on YM formula, assessment of tissue elasticity can be derived from shear wave propagation velocity, where elasticity is proportional to the square of shear wave propagation velocity (Equation 6) [30].

The shear waves generated must be tracked by the ultrasound system. Ultrasfast imaging image the entire propagating wave with good temporal resolution in a single acquisition by reaching frame rates of 5000 to 30000 images per second [3]. Therefore, it allows complete acquisition without repetition for the entire displacement field and can be displayed in real-time, much like conventional ultrasound images. The YM map are then reconstructed by estimating

the speed of the shear wave between two points in the image, using a time-of-flight algorithm [31].

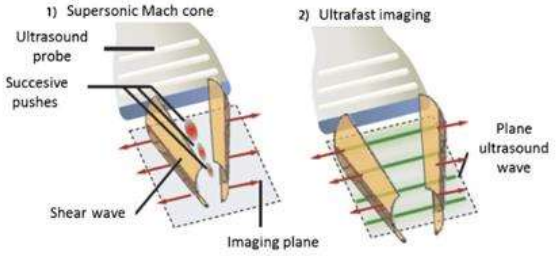

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Fig 6 Ultrasound beams are successively focused at different paths to create push force by radiation pressure. The constructive interference of the shear waves forms a Mach cone, in which the speed of the source is higher than the speed of the generated wave, and a quasi-plane shear wave is created (a) (Gennisson, 2013).

Clinical Applications of 2DSWE

Compared to transient elastography and pSWE, the application of 2DSWE is more extensive which include superficial and deep structures. This technique is replacing strain elastography in breast imaging rapidly due to its high reproducibility rate and the availability of absolute stiffness value. According to Youk, et al. [32], 2DSWE is now an adjunct tool in breast ultrasonography. One of the advantages of SWE is the characterization of breast masses that are categorized as BI-RADS 3 and 4a, to avoid unnecessary breast biopsies [33, 34]. The combination of SWE with conventional B-mode ultrasound increases the diagnostic performance in characterize breast lesions, compared with conventional B-mode ultrasound alone. Furthermore, SWE can provide additional information on predicting breast cancer prognosis and response to neoadjuvant chemotherapy (NAC). Lesion stiffness is related to the collagen content in the stroma, stromal stiffness measured by SWE could serve as a potential imaging biomarker for stromal structural abnormalities and the response to NAC [35].

Among the shear wave elastography techniques, 2DSWE has the highest sensitivity in detection of significant fibrosis and advanced fibrosis [36, 37]. Based on a phantom study by Leong, et al. [38], 2DSWE is more accurate than pSWE when compared with dynamic mechanical analysis, the reference standard. One of the possible justifications to these results could be the technical factor. Unlike pSWE, 2D SWE could produce a 2D elastogram, a colour-coded map or a confidence map reflecting tissue stiffness is displayed (Fig. 7). This allowed operators to obtain stiffness measurements from an area with the best shear wave quality (homogeneity and temporal stability) [39]. This provided an effective guide to obtain better image quality and reduce measurement variability.

In 2DSWE, dynamic stress is induced by ARFI in multiple focal zones. This allows a real-time monitoring of shear wave for stiffness measurements at several locations at one image acquisition. This has overcome the breath hold challenge encountered by patients, especially to those who have shortness of breath.

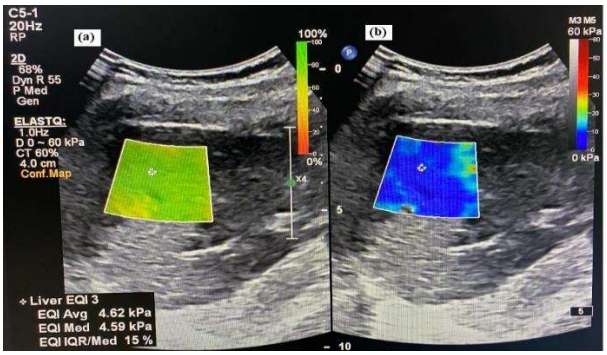

Fig 7 (a) colour-coded confident map indicates area with the best shear wave quality (homogeneity and temporal stability). (b) 2DSWE of liver with tissue stiffness expressed either in kPa or m/s. Note elastogram is available in 2D SWE.

IV. CONCLUSION

Ultrasound- based elastography is widely available and easy to operate in a clinical setting. The fact that ultrasound-based elastography can be done bedside along with the B-mode examination (except transient elastography) enables the application of elastography feasible in a lot of different anatomic areas. Although the outcome of ultrasound- based elastography is encouraging, standardized scanning protocol and validated for each elastography device should be proposed and applied to provide a more accurate diagnostic performance in differentiating normal and disease organ/ lesions.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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